REMARKS

Claims 35, 37-42, 44-55, and 57 have been amended to improve the clarity of the claims and/or to improve antecedent basis. No new matter has been added.

The Final Office Action mailed April 1, 2005, has been received and reviewed. Claims 35, 37-42, 44-55, and 57 are currently pending in the application. Claims 35, 37-42, 44-55, and 57 stand rejected. Applicants have amended claims 35, 37-42, 44-55, and 57 and respectfully request reconsideration of the application as proposed to be amended herein and in light of the Rule 132 Declaration filed with the instant response.

Rule 132 Declaration

During a telephone call with Applicants' representative, Examiner Channavajjala agreed that Applicants could submit a Rule 132 Declaration to address the remaining rejections, even though the pending Office Action is "final," as long as the Rule 132 Declaration does not raise new issues or submit new data. Applicants submit that submission of the Rule 132 Declaration is proper now because Applicants had no reason to believe that such a submission was necessary or appropriate with the response filed December 9, 2004. That is, the discussion of the obviousness rejections with the Examiner during the interview held on November 30, 2004, prompted Applicants to believe that the explanations and claim amendments submitted with the response filed December 9, 2004, would overcome the obviousness rejections. As such, Applicants were surprised to receive the instant Final Office Action maintaining the same rejections. Therefore, Applicants respectfully urge that the Examiner consider the Rule 132 Declaration filed with the instant response.

35 U.S.C. § 103(a) Obviousness Rejection

Obviousness Rejection Based on WO 99/44623 to Artman *et al.* in view of U.S. Patent No. 4,571,333 to Hsiao *et al.*

Claims 35, 37-39, 41, 42, 47, 51-54, and 57 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over WO 99/44623 to Artman *et al.* ("Artman") in view of U.S. Patent No. 4,571,333 to Hsiao *et al.* ("Hsiao"). Applicants respectfully traverse this rejection, as hereinafter set forth.

M.P.E.P. 706.02(j) sets forth the standard for an obviousness rejection:

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

The obviousness rejection of claims 35, 37-39, 41, 42, 47, 51-54, and 57 is improper because the cited references do not provide a motivation to combine to produce the claimed invention and do not provide a reasonable expectation of success.

Artman teaches a combination therapy that includes a valerian-related compound and a nonsteroidal antiinflammatory drug ("NSAID"). The valerian-related compound includes a preparation or extract of valerian, such as isovaleramide, isovaleric acid, or a pharmaceutically acceptable salt, ester, or substituted amide thereof. The combination therapy is formulated into a pharmaceutical composition that is a solid or liquid oral dosage form, such as a tablet, a capsule, a gelcap, a powder, a concentrate, an elixir, a tincture, or a syrup.

Hsiao teaches a sustained-release formulation of naproxen. The sustained-release formulation includes 81-96 weight percent of naproxen in a matrix of 4-9 weight percent hydroxypropylmethylcellulose.

The cited references do not provide a motivation to combine to produce the invention of independent claims 35 and 51. To provide a motivation or suggestion to combine, the prior art or the knowledge of a person of ordinary skill in the art must "suggest the desirability of the combination" or provide "an objective reason to combine the teachings of the references." M.P.E.P. § 2143.01. The mere fact that references <u>can</u> be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *Id.* (emphasis in original).

Applicants respectfully submit that the cited references do not suggest the desirability of the combination or provide an objective reason to combine. As acknowledged by the Examiner,

Hsiao does not teach or suggest an oral sustained-release pharmaceutical composition that comprises the recited active compounds of claims 35 and 51 because Hsiao does not teach or suggest any of the active compounds. Office Action of April 1, 2005, p. 2. Therefore, Hsiao necessarily does not teach or suggest that such an active compound is present in the oral sustained-release pharmaceutical composition in an amount of from about 40% to about 70% by weight. As acknowledged by the Examiner, Artman does not teach or suggest an oral sustained-release pharmaceutical composition that comprises a gelling agent. *Id.* at p. 3. Therefore, the Examiner relies on the combination of Artman and Hsiao to teach all of the limitations of independent claims 35 and 51. The Examiner states that "it would have been obvious for one of an ordinary skill in the art at the time of the instant invention to prepare the composition of [Artman] . . . in the form of an oral sustained release matrix by adding a sustained release swelling agent, HPMC, because Hsiao teaches that the pain or inflammation treating composition prepared in a matrix with HPMC prolongs the release of the active agent so as to achieve a once-a-day administration." *Id.* The Examiner also states that "it would have been obvious for a skilled artisan at the time of the instant invention to add valerian extracts, isovaleramide etc. to the anti-inflammatory naproxen containing composition of Hsiao because [Artman] suggests that the combination treats inflammation as well as provides a relief from acute pain and muscular tension" and that it would have been obvious "to add HPMC of Hsiao to the composition of [Artman] . . . because Hsiao teaches that the composition prepared in a matrix with HPMC prolongs the release of the active agent." *Id.* at p. 3 and p. 6.

However, these statements by the Examiner are conclusory and are not based on objective evidence of record because nothing in the cited references, when combined, suggests the desirability of the combination or provides an objective reason to combine. In addition, as described below and in the accompanying Rule 132 Declaration, the Examiner's statements reflect a reading of Hsiao that is too broad and that overlook specific teachings in Hsiao that demonstrate that there would have been no motivation to combine the cited references to produce the claimed invention.

Specifically, nothing in Artman suggests the desirability of the combination or provides an objective reason to combine because Artman does not provide any teaching or suggestion that a sustained-release pharmaceutical composition comprising the recited active compound and the

gelling agent would be desirable. As described in the Rule 132 Declaration (see ¶4-¶6) and at p. 2 and 5 of the as-filed specification, the inventors of the above-referenced patent application recognized the short *in vivo* half-life of isovaleramide during the first human clinical trial of isovaleramide. Without the data generated during this human clinical trial, a person of ordinary skill in the art would not have expected that a sustained-release formulation of isovaleramide would be necessary. In other words, before this discovery by the inventors of the above-referenced patent application, there was simply no reason to provide the recited active compounds in a sustained-release composition. The prior knowledge of isovaleramide compositions (*e.g.*, as taught in Artman) and of sustained-release compositions for naproxen (*e.g.*, as taught in Hsiao) do not render obvious the claimed sustained-release pharmaceutical composition and the claimed method of treating a pathology because a person of ordinary skill in the art would have had no reason to formulate any of the recited active compounds into a sustained-release composition. Hsiao also does not suggest the desirability of the combination or provide a motivation to combine because Hsiao teaches that sustained release formulations are active agent specific and Hsiao does not teach or suggest that the controlled release formulations taught therein would be relevant to any other active agent, such as one of the recited active compounds in claims 35 or 51. Rather, the teachings of Hsiao are limited to a sustained-release formulation of naproxen. Applicants respectfully submit that only Applicants' present teachings provide such motivation, by recognizing the short half-life of the claimed compounds *in vivo*. Therefore, the Examiner's stated motivation to combine appears to be impermissibly based on hindsight.

Furthermore, Hsiao teaches away from combination with Artman because Hsiao teaches that the development of a sustained-release composition is specific to the active agent. See, Hsiao at column 3, lines 6-23 and the Rule 132 Declaration ¶7-¶8. Hsiao expressly teaches that "different types of controlled release oral dosage forms have been developed, but each has disadvantages which affect its suitability **to a particular drug**." *Id.* at column 3, lines 6-9 (emphasis added). Hsiao also states that "[w]ide variations in the physico-chemical and pharmacokinetic properties of different drugs impose such varied requirements on the design of controlled drug delivery formulations, that formulations that are suitable for one drug **cannot generally be predictably applied to other drugs**." *Id.* at column 3, lines 9-14 (emphasis

added). Therefore, one of ordinary skill in the art, after reading Artman and Hsiao, would not be motivated to combine these references to produce the claimed invention.

Furthermore, even if the cited references were combined, the claimed invention would not be produced. As previously described, the sustained-release formulation of naproxen in Hsiao includes 81-96% by weight of naproxen. Hsiao only teaches sustained-release compositions of naproxen and naproxen sodium and does not teach or suggest a sustained-release composition of another active agent, such as a sustained-release composition of one of the recited active compounds. Accordingly, the tablets of Hsiao could not also contain from about 40% to about 70% by weight of the active compound, as recited in the instant claims. Although Artman teaches compositions that include isovaleramide and naproxen, Artman does not teach or suggest that these compositions are a sustained-release formulation, let alone sustained-release compositions that comprise from about 40% to about 70% by weight of one of the recited active compounds.

In addition, as acknowledged by the Examiner, Hsiao could not be modified to produce the claimed invention because the tablets of Hsiao includes from 81-96% by weight naproxen, which is a substantially higher concentration of the active compound than is recited in claims 35 and 51. Office Action of April 1, 2005, p. 5-6. Accordingly, even if Artman and Hsiao were combined, the resulting pharmaceutical composition would not include from about 40% to about 70% by weight of one of the recited active compounds. Furthermore, as evidenced in the Rule 132 Declaration, there is no teaching or suggestion in the cited references that would have lead a person of ordinary skill in the art to produce an oral sustained-release pharmaceutical composition that comprises from about 40% to about 70% by weight of one of the recited active compounds. See, the Rule 132 Declaration ¶10.

In addition, based on the teachings of Artman and Hsiao, there is no reasonable expectation of success of achieving an oral sustained-release pharmaceutical composition as recited in claim 35 and in the method of claim 51. As previously described, the Examiner's statements reflect a broad reading of Hsiao that overlooks specific teachings that demonstrate that there would have been no expectation of success. Since Hsiao explicitly teaches that developing a sustained-release composition is specific to the active agent, a person of ordinary skill in the art, upon reading Hsiao, would not have reasonably expected that adding HPMC

according to the teachings of Hsiao to the compositions of Artman would produce a workable oral sustained-release composition that includes each of the characteristics recited in the pending claims. See, the Rule 132 Declaration ¶7-¶10.

Since the cited references do not provide a motivation to combine to produce the claimed invention and there is no reasonable expectation of success, the obviousness rejection of independent claims 35 and 51 is improper and should be withdrawn.

Dependent claims 37-39, 41, 42, 47, 52-54, and 57 are allowable, *inter alia*, as depending from an allowable base claim.

Obviousness Rejection Based on Hsiao in view of Artman or Artman in view of Hsiao and further in view of "Development of Optimal Intestine-Soluble Film-Forming Acetylphthalylcellulose-Based Compositions for Fluidized-Bed Coating of Tablets," to Groshovy *et al.*, Pharmaceutical Journal, No. 2 (1975)

Claims 40, 44-46, 48-50, and 55 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Hsiao in view of Artman or Artman in view of Hsiao and further in view of "Development of Optimal Intestine-Soluble Film-Forming Acetylphthalylcellulose-Based Compositions for Fluidized-Bed Coating of Tablets," to Groshovy *et al.* ("Groshovy") Pharmaceutical Journal, No. 2 (1975). Applicants respectfully traverse the rejection as to the remaining claims, as hereinafter set forth.

The teachings of Artman and Hsiao are as previously described.

The Examiner relies on Groshovy as teaching a "coating of tablets with intestine soluble film forming polymer such as acetylphthalylcellulose . . . . Groshovy teaches tablets containing valerian extracts are usually destroyed by gastric juices in two hours and the resulting weight loss prompts the addition of plasticizers to the film-forming substances." Office Action of April 1, 2005, p. 4.

The obviousness rejection of claims 40, 44-46, 48-50, and 55 is improper because the cited references do not provide a motivation to combine to produce the claimed invention and do not provide a reasonable expectation of success.

The cited references do not provide a motivation to combine to produce the invention of independent claim 48 and do not provide a reasonable expectation of success. Artman and Hsiao

do not provide a motivation to combine and a reasonable expectation of success for substantially the same reasons as discussed above in the obviousness rejection of independent claims 35 and 51. Specifically, since Artman and Hsiao do not provide a motivation to combine to produce an oral sustained-release pharmaceutical composition, Artman and Hsiao necessarily do not provide a motivation to combine to produce a process of preparing such an oral sustained-release pharmaceutical composition. Since Groshovy is limited to the teachings described above, Groshovy does not cure the deficiencies in Artman and Hsiao and, therefore, does not provide a motivation to combine and a reasonable expectation of success.

Since the cited references do not provide a motivation to combine to produce the claimed invention and there is no reasonable expectation of success, the obviousness rejection of independent claim 48 is improper and should be withdrawn.

Claims 40 and 44-46 depend on claim independent 35, claims 49 and 50 depend on independent claim 48, and claim 55 depends on independent claim 51. Since each of these dependent claims includes all of the limitations of the respective independent claim, each of dependent claims 40, 44-46, 49, 50, and 55 is allowable, *inter alia*, as depending from an allowable base claim.

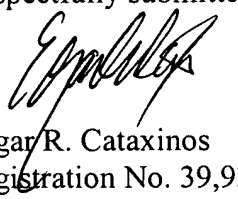
ENTRY OF AMENDMENTS

The proposed amendments to claims 35, 37-42, 44-55, and 57 should be entered by the Examiner because the amendments are supported by the as-filed specification and drawings and do not add new matter. Further, the amendments do not raise new issues or require a further search. Finally, if the Examiner determines that the amendments do not place the application in condition for allowance, entry is respectfully requested upon filing of a Notice of Appeal herein.

CONCLUSION

Claims 35, 37-42, 44-55, and 57 are believed to be in condition for allowance, and an early notice thereof is respectfully solicited. Should the Examiner determine that additional issues remain that might be resolved by a telephone conference, the Examiner is respectfully invited to contact Applicants' undersigned attorney.

Respectfully submitted,



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Date: September 30, 2005
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